Malaria parasites: elimination is not eradication

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For those of us who participate in the fight against malaria, the present time stands in stark contrast to what we have always known. In comparison with the eve of this century, less than a dozen year ago, there is presently some unanimously accepted good news. The global burden of malarial disease has been reduced in a large variety of settings, regardless of transmission intensities and endemic patterns. Malaria prevalence, morbidity and mortality are now low enough in several areas of tropical Africa to challenge some well-established principles of malariology.

There are three major reasons for this welcome improvement: (i) the unprecedented increase in funding devoted to malaria control; (ii) generalization of the shift from chloroquine to artemisinin-based combination therapy for the treatment of clinical malaria attacks; and (iii) deployment of a much better prevention strategy, largely owing to insecticide-treated bed-nets and, in some places, to residual wall spraying with insecticides.

Two other approaches also proved to be very effective where they were deployed: intermittent preventive treatment, probably equivalent to targeted chemoprophylaxis, focused at the two most vulnerable populations—pregnant women and children; and improvement of case detection with rapid diagnostic test kits that are easily usable at the patient's bedside by both local health workers and nurses.

Although prompt access to effective drugs has been shown to prevent most malaria deaths, even in a context of intense malaria transmission, and the implementation of insecticide-treated nets has dramatically reduced the burden of malaria, there is no doubt that the combination of different interventions has had a synergistic effect, resulting in a much higher impact than the separate use of individual control measures.

Forty countries worldwide have recently reduced malaria deaths and cases by half. Some countries, such as Morocco, have recently eliminated malaria completely, and others have made impressive progress, such as South Africa and Swaziland, where cases have decreased by approximately 90%. A recent report on malaria research underlines that investment has more than quadrupled in the past 16 years, from US$121 million in 1993 to US$612 million in 2009 [1]. Between 2004 and 2009, 28% of this funding was used for vaccine development, 38% for new drugs or combinations of drugs, 23% for basic research, but only 4% for vector control products (mainly new insecticides) and 1% for new diagnostic testing systems. This contrasting picture largely reflects the donor funding preferences.

In this special issue of *Clinical Microbiology and Infection*, devoted to malaria elimination, Brian Greenwood and Geoffrey Targett provide definitions of malaria control, elimination and eradication, before they focus on malaria vaccines and explain why second-generation vaccines are needed even though the first malaria vaccine has not yet been licensed [2]. Meredith McMorrow [3] emphasizes the importance of malaria diagnostic tests in the context of elimination, and discusses how these tests are useful and what improvements are needed in the future. Roly Gosling, Lucy Okell, Jacklin Mosha and Daniel Chandramohan express their views on active case detection and malaria treatment for clinical cases, as well as asymptomatic parasite carriers. Unsurprisingly, modelling approaches advocate maximum efficacy when drug administration programmes are implemented at the same time as antivector activities [4]. Kaliyaperumal Karunamoorthi [5] focuses on vector control measures. Since the pioneering studies that discovered the efficacy of bed-nets when they were treated by dipping them in pyrethroid insecticides [6,7], long-lasting factory-coated or impregnated bed-nets have been developed that do not need to be repeatedly impregnated. Indoor and/or outdoor residual spraying with insecticides constitutes the second main tool for vector control. Many other vector control tools exist, but are used on a much smaller scale or remain at the stage of proof-of-concept [8].

The remarkable successes achieved in malaria elimination must not be allowed to disguise their delicate nature [9]. Elimination, by definition, implies that both capacity and commitment are needed to sustain this status indefinitely [10].

The major current potential barrier to malaria elimination lies within uncertainties concerning the durability of funding: only two organizations, the Bill and Melinda Gates Foundation and the US National Institutes of Health, provided half of the global malaria research and development funding in 2007–2009 [1]. Malaria control activities are mainly funded by multilateral or bilateral initiatives, including the Global Fund, the World Bank Malaria Booster Program, and the US President's Malaria Initiative, that depend heavily on the involvement of the governments of developed nations and are therefore subject to changing political and economic priorities. There is an urgent need for new innovative and sustainable financing mechanisms, such as the UNITAID initiative (http://www.unitaid.eu), launched by France and Brazil in 2006 (UNITAID groups 29 committed countries, receives its funds through airline ticket taxes or regular budget contributions, and contributes to the scaling up of access to treatment in the poorest countries).

A second concern is resistance to artemisinin, which has been detected in the region of the Thai/Cambodia border, underlining the ongoing need for new drugs/combined therapies. In parallel, the increase in the pan-global detection of pyrethroid resistance in a number of populations of malaria vectors is also worrying, as recently established in Senegal, where a rebound in malaria morbidity following the emergence of pyrethroid resistance in *Anopheles gambiae* was observed [11]. The fragility of the available tools for fighting malaria, and the need for the development of new tools to achieve *Plasmodium falciparum* elimination, must be recognized. This is the case in tropical Africa, where control is not easy, mainly because the anopheline vectors are the most efficient in the world. *A. gambiae* exhibits a huge and challenging vectorial capacity: even very low gametocyte frequencies in the community may sustain high entomological inoculation rates where this vector is present. Achievement of *Plasmodium vivax* elimination is subject to another set of problems, mainly because of the dormant hypnozoite stage and the limitations of primaquine, the only available drug against the liver-stage parasite [12].

A third concern is our lack of knowledge. A major gap is our poor understanding of the mechanisms and conditions of the likely rebound or resurgence of disease if control measures are reduced. Historical observations in Ethiopia [13] and Sri Lanka [14] have shown how the malaria situation can worsen rapidly and dramatically in the context of unanimously recognized successes. Vast areas of uncertainty remain to be investigated, such as: the importance of heterogeneity of contact between humans and mosquitoes, resulting in a small proportion of people receiving a large proportion of parasite inoculations; *Plasmodium* transmission by exophilic vectors; the potential reservoir of human-infective parasites in apes and monkeys; the R_0 (the basic reproductive number, i.e. the number of secondary cases of malaria arising from a single case) in a context of near-zero immunity; and the capacity of mass drug administration for elimination-specific intervention.

Once elimination has been achieved, measures aimed at preventing imported infections must be implemented and maintained. These measures imply coercive interventions that are only possible if public health administration is sufficiently stringent and effective. Some isolated areas (e.g. islands such as Mauritius, Zanzibar and Bioko, or northern Africa vs. tropical Africa, with restricted exchanges owing to the natural boundary of the Sahara) may be less vulnerable to re-invasion. A more negative scenario is where neighbouring countries have very different and perhaps incompatible control/elimination statuses, leading to much more complex situations with a high frequency of re-invading malarial parasites via both infected people and mosquitoes.

Because maintenance of the measures requires strong and stable governments, achieving and maintaining elimination cannot be considered independently of the social and political developments in malaria-endemic countries. These developments constitute a necessary condition for malaria elimination that lies outside the present scope of any malaria elimination programme.

Today, some 67 countries worldwide are involved in the control of endemic malaria; 32 are considered to be malaria-eliminating countries, with the dominant challenge of eliminating *P. vivax* parasites, and a further 109 countries are malaria-free (79 of which have eliminated malaria since 1945). Prominent colleagues [15] accept that all malaria-eliminating countries have a reasonable prospect of achieving elimination within the next decade or so. In many other countries, it seems feasible to eliminate malaria transmission in highland, mountainous, semi-arid and urbanized areas [16]. The massive urbanization process that has been occurring in Africa since the mid-1960s is likely to improve the prospects for malaria elimination on a local scale [17], because more and more people will live with a lower risk of infection. They should then be considered as non-immune travellers when moving elsewhere within the country, i.e. be subject to prophylactic measures recommended to travellers [18].

There is growing evidence that elimination of the transmission of the malarial parasites, at national or subnational levels, is occurring. This is a great cause for celebration in

the short term. However, bearing in mind the lessons of the past [19], no one envisions a future in which eradication is a certainty.

Talking prematurely of malaria eradication is a double-edged sword. Positive aspects are numerous, and among them are: the necessary reminder that eradication is the final goal; and the fact that civil society, the political community and the fund donors easily understand the concept [20]. In Seattle in October 2007, Melinda Gates rightly proclaimed in her address to researchers and policy-makers from around the world: 'Bill and I believe that these advances in science and medicine, your promising research, and the rising concern of people around the world represent a historic opportunity not just to treat malaria or to control it—but to chart a long-term course to eradicate it.' Unfortunately, negative aspects are also numerous: talk of eradication implies that the tools and knowledge needed to achieve the objective will be available in any country and situation, and that eradication can be readily achieved without exception around the world. To avoid huge disappointment, those actively working towards malaria elimination must maintain realistic expectations. They must be aware of the limitations of their interventions, especially with regard to their durability and maintenance, without a defined endpoint in a changing and unstable world.

Transparency Declaration

V. Robert, J. F. Trape and C. Rogier have permanent positions in French national institutes of research. The authors declare no conflicts of interest.

References

1. PATH. *Staying the course? Malaria research and development in a time of economic uncertainty*. Seattle: Program for Appropriate Technology in Health, 2011.
2. Greenwood BM, Targett GAT. Malaria vaccines and the new malaria agenda. *Clin Microbiol Infect* 2011; 17: 1600–1607.
3. McMorrow ML, Aidoo M, Kachur SP. Malaria rapid diagnostic tests in elimination settings—can they find the last parasite? *Clin Microbiol Infect* 2011; 17: 1624–1631.
4. Gosling RD, Okell L, Mosha J, Chandramohan D. The role of antimalarial treatment in the elimination of malaria. *Clin Microbiol Infect* 2011; 14: 1617–1623.
5. Karunamoorthi K. Vector control: a cornerstone in the malaria elimination campaign. *Clin Microbiol Infect* 2011; 17: 1608–1616.
6. Darriet F, Robert V, Tho Vien V, Carnevale P. Evaluation de l'efficacité sur les vecteurs de paludisme de la perméthrine en imprégnation sur les moustiquaires intactes et trouées. WHO/VBC/84.899 or WHO/MAL/84.1008.
7. Ranque P, Touré YT, Soula G *et al.* Étude expérimentale sur l'utilisation de moustiquaires imprégnées de deltaméthrine dans la lutte contre le paludisme. *Parassitologia* 1984; 26: 261–268.
8. The malERA Consultative Group on Vector Control. A research agenda for malaria eradication: vector control. *PLoS Med* 2011; 8: e1000401.
9. Moonen B, Cohen JM, Snow RW *et al.* Operational strategies to achieve and maintain malaria elimination. *Lancet* 2010; 376: 1592–1603.
10. Cohen JM, Moonen B, Snow RW, Smith DL. How absolute is zero? An evaluation of historical and current definitions of malaria elimination. *Malaria J* 2010; 9: 213.
11. Trape JF, Tall A, Diagne N *et al.* Rebound and age shift in malaria morbidity two years after the implementation of insecticide-treated nets in a West African population receiving artemisinin-based combination therapy. *Lancet Infect Dis* 2011; 11: Aug 18 [Epub ahead of print].
12. Rughani G. Development of 50 malaria drugs is under threat unless funding expands. *BMJ* 2011; 342: d4158.
13. Fontaine RE, Najjar AE, Preince JS. The 1958 malaria epidemic in Ethiopia. *Am J Trop Med Hyg* 1961; 10: 795–803.
14. Wijesundera MS. Malaria outbreaks in new foci in Sri Lanka. *Parasitol Today* 1988; 4: 147–150.
15. Feachem RGA, Phillips AA, Hwang J *et al.* Shrinking the malaria map: progress and prospects. *Lancet* 2010; 376: 1566–1578.
16. Trape JF, Pison G, Spiegel A, Enel C, Rogier C. Combating malaria in Africa. *Trends Parasitol* 2002; 18: 224–230.
17. Machault V, Vignolles C, Pages F *et al.* Spatial heterogeneity and temporal evolution of malaria transmission risk in Dakar, Senegal, according to remotely sensed environmental data. *Malar J* 2010; 9: 252.
18. Baragatti M, Fournet F, Henry MC *et al.* Social and environmental malaria risk factors in urban areas of Ouagadougou, Burkina Faso. *Malar J* 2009; 8: 13.
19. World Health Organization. *Re-examination of the global strategy of malaria eradication*. Geneva: WHO, 1969.
20. Mendis K, Rietveld A, Warsame M *et al.* From malaria control to eradication: the WHO perspective. *Trop Med Int Health* 2009; 14: 802–809.